Sturge-Weber Syndrome Without Cutaneous Stigmata Versus Encephalocraniocutaneous Lipomatosis Without Craniocutaneous Lipomatosis: A Case Report

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ABSTRACT

Introduction: Sturge-Weber syndrome and encephalocraniocutaneous lipomatosis (ECCL) are neurocutaneous syndromes with unique presentations.

Case Presentation: A 15-month-old male presented with focal seizures that progressed to medically refractory focal epilepsy. He had no ocular or cutaneous findings. Imaging demonstrated complex, transdural leptomeningeal enhancement suspicious for pial angiomatosis. Electroencephalogram showed focal seizures from the right posterior region. Sturge-Weber syndrome without cutaneous manifestations was suspected. Following right posterior disconnection surgery, next generation sequencing of affected brain tissue confirmed a mosaic *FGFR1* variant, confirming the diagnosis of ECCL.

Discussion: ECCL may have variable expression and should be considered in children with refractory epilepsy and an anatomical brain abnormality.

Conclusions: Leptomeningeal enhancement is commonly found in Sturge-Weber syndrome but may be seen in other neurocutaneous syndromes, such as ECCL. Hemispheric dysplasia should raise suspicion for a neurocutaneous syndrome, even without oculocutaneous stigmata. Genotype-guided diagnostics for patients with atypical findings may facilitate targeted postsurgical management and lifetime surveillance.

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INTRODUCTION

Epilepsy is a chronic neurologic condition that involves recurrent seizures. A study of children in the United States estimated that 10.2 per 1000 children developed epilepsy at some point during their first 18 years of life.[1] While most will have cessation of seizures with medical treatment, 9% to 23% of children with epilepsy will continue to have seizures despite trials of different medications alone or in combination,[2] termed refractory (or drug-resistant) epilepsy.[3] Neurocutaneous conditions are one of many causes of refractory epilepsy in children.[2]

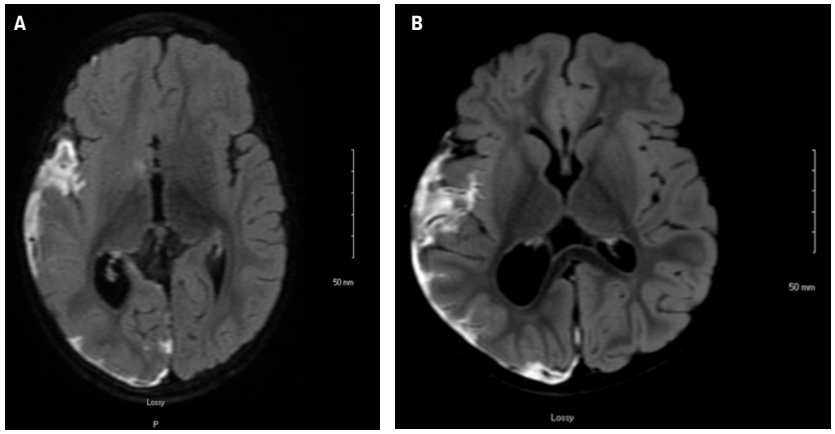
Sturge-Weber syndrome (SWS) is a rare congenital neurocutaneous condition typically characterized by a port-wine birthmark, glaucoma, seizures, and leptomeningeal angiomatosis.[4] It is estimated to occur at a frequency between 1 in 20 000 and 1 in 50 000 live births and is associated with postzygotic mutations in the *GNAQ* and *GNA11* genes.[4] A novel variant in the *GNB2* gene, encoding a beta chain of the *GNAQ* G-protein complex, was also recently discovered.[5] It is theorized that the scope of tissues affected is based on when the causative mutation arose during development (the later the mutation occurrs, the more likely fewer tissues are involved).[6] Seizures and neurologic injury are often progressive in SWS. When seizures prove to be medically refractory, it is essential to evaluate for epilepsy surgery as early as possible to optimize developmental outcomes.[7]

While a segmental port wine birthmark involving the forehead region is often the first clue leading to a diagnosis of SWS, patients have been described as having SWS based only on

neuroimaging findings, without cutaneous involvement.[7] SWS without cutaneous manifestations remains incompletely defined. Its prevalence is poorly understood, and descriptions are limited to case reports or series—all without genomic confirmation.[8-11] Confirmation of genetics requires a biopsy of the affected tissue (skin in classic SWS, but brain in SWS without cutaneous manifestations).

Here, we present the case of a boy with medically refractory focal epilepsy who, based on neuroimaging, initially was thought to have SWS without cutaneous manifestations. However, next generation sequencing of biopsied brain tissue demonstrated mosaicism of an activating *FGFR1* variant, suggesting a genetic diagnosis of encephalocraniocutaneous lipomatosis (ECCL), despite the absence of craniocutaneous lipomatosis.

Figure 1. Axial FLAIR Image



A. Axial FLAIR image demonstrating right cerebral hemiatrophy with associated enlargement and enhancement of subarachoid spaces and expansion of right hemicalvaria.

B. Repeat imaging 4 months after initial presentation with similar findings of complexity of the right subarachnoid space and abnormal enhancement suggestive of leptomeningeal angiomatosis.

Abbreviation: FLAIR, fluid attenuated inversion recovery.

CASE PRESENTATION

An otherwise healthy 15-month-old male presented with new onset seizures. He had no notable medical history and no known history of seizures. On the day of his initial presentation, he had sustained an unwitnessed fall from a 1.5-foot tall stool onto a hard floor. It was unknown if he had lost consciousness or hit his head, but he appeared normal after the fall. He took a longer nap than usual that afternoon and was found in bed coughing, laying in vomit, and with decreased responsiveness. Emergency medical services were called, and he was transported to an outside hospital, where he was found to have abnormal movements with unilateral extremity rigidity. Initial head imaging at the outside hospital identified a subdural fluid collection, enlarged fourth ventricle, and bilateral ventriculomegaly (right greater than left). He was given antiseizure medications and transported to our institution for further evaluation.

Subsequent imaging demonstrated asymmetric right hemi-calvarial enlargement, right hemispheric atrophy, right lateral ventricular enlargement, enlargement of right cerebral subarachnoid spaces, and scattered areas of right frontal pial and leptomeningeal enhancement (Figure 1). Given these findings, it was determined that the patient's focal status epilepticus was likely a result of a chronic neurologic process rather than an acute traumatic event. The structural variations identified in imaging were suspected to be developmental or genetic in nature.

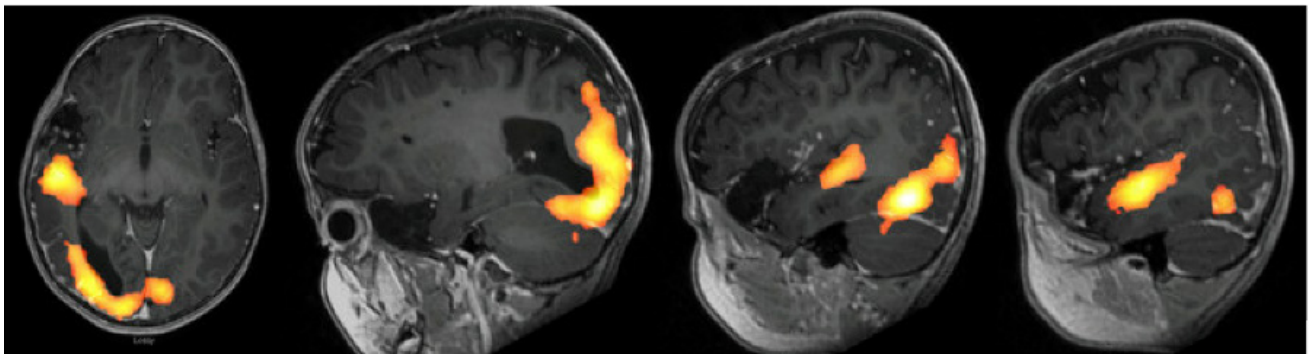
Detailed ophthalmologic and dermatologic exams did not reveal any abnormalities. Continuous electroencephalogram (EEG) obtained over 21 hours during his initial hospitalization did not reveal any additional seizures but was notable for background asymmetry with lower amplitudes in the right posterior head region. The patient was discharged on levetiracetam monotherapy.

Despite antiseizure medication therapy, the patient's epilepsy was persistent and progressive. He had multiple episodes of status epilepticus requiring hospitalization with medication escalation. Oxcarbazepine was added to his antiseizure medication regimen, but he continued to have breakthrough prolonged seizures triggered by illness. He underwent repeat magnetic resonance imaging 5 months after his initial presentation, which suggested evidence of leptomeningeal angiomatosis associated with progressive gliosis and atrophy within the right hemisphere, as well as stable hypoperfusion on the right side. Scalp EEG studies showed evidence of focal onset seizures from the right posterior region, with interictal activity over the same distribution.

Throughout this period, the patient had normal development and did not demonstrate any cutaneous or ocular findings. Given the imaging findings and epilepsy progression, it was suspected that he most likely had SWS without cutaneous manifestations.

Due to the progressive clinical course, difficulty controlling seizures with multiple antiseizure medications, and suspected diagnosis of SWS without cutaneous manifestations, a surgical workup was recommended and obtained 21 months following his initial presentation. EEG showed multiple focal seizures with right occipital onset with secondary generalization, and no abnormal activity was noted on the left side; subtraction ictal-interictal single-photon emission computed tomography (SPECT) showed uptake within the right temporal lobe and right occipital lobe (Figure 2); and positron emission tomography (PET) showed

Figure 2. Subtraction Ictal-interictal SPECT- demonstrated Uptake Within the Right Temporal Lobe and Right Occipital lobe



Abbreviation: SPECT, single-photon emission computed tomography

hypometabolism in the right temporal lobe. Surgical intervention with a posterior disconnection and/or complete hemispherectomy was recommended.

The family sought independent consultation from 2 pediatric epilepsy centers. Their consensus opinion was consistent with the diagnosis of SWS without cutaneous manifestations and recommended treatment was to proceed with a posterior disconnection surgery, holding in reserve a full right hemispheric disconnection in the event of seizure recurrence postoperatively.

Twenty-three months after the patient's initial presentation (at age 3 years and 3 months), he underwent a right craniotomy for posterior quadrantectomy with temporoparietal and occipital disconnection (see intraoperative findings in Figure 3). Gross examination of the cortical surface indicated an abnormal leptomeningeal appearance (Figure 3A). Neurophysiological monitoring for motor mapping was undertaken to localize and preserve motor function (Figure 3A). A complete temporal-parietal-occipital disconnection was undertaken (Figure 3B). Biopsy samples were taken from his right temporal lobe and sent for next generation sequencing of 277 genes implicated in vascular anomalies. The patient tolerated this procedure well. He had transient left hemibody weakness for the first 48 hours postoperatively that resolved spontaneously, and he was discharged home on levetiracetam and lacosamide.

On histopathology, the affected tissue showed nerve cell loss and severe gliosis/sclerosis with no findings consistent with vascular involvement or angiomatosis, encephalitis, or vasculitis. Next generation sequencing of tissue demonstrated a pathogenic *FGFR1* gene mutation, c.1638C>A (p.Asn546Lys), consistent with ECCL. This involved *FGFR1* mosaicism in the central nervous system (CNS), with 4.4% of cells affected by the genetic variant and a low percentage of affected cells indicating mild disease.

The patient has continued treatment with levetiracetam and lacosamide maintenance therapy and has not had recurrence of seizures in the 12 months following surgery. Follow-up overnight video EEG showed right hemispheric epileptiform discharges around the surgical resection site and generalized epileptiform discharges of uncertain clinical significance. He has continued to meet developmental milestones and will be followed with routine imaging, dental care, and ophthalmologic examinations.

DISCUSSION

Our patient was suspected to have Sturge-Weber syndrome without cutaneous manifestations due to the progressive nature of his focal epilepsy and leptomeningeal enhancement on imaging. Upon next generation sequencing of tissue obtained during epilepsy surgery, he was found to have a pathogenic variant in *FGFR1* associated with ECCL. The hallmarks of ECCL are characteristic cutaneous, ocular, and CNS manifestations.[12] Our patient presented only with CNS manifestations (seizures and structural changes on imaging) and, therefore, did not fulfill the clinical diagnostic criteria for ECCL. This is the first patient to our knowledge with isolated CNS manifestations of ECCL, and the diagnosis relied on next generation sequencing of affected tissue.

Postzygotic pathogenic mutations in the *FGFR1* and *KRAS* genes cause ECCL.[12] Because the disease is mosaic, sequence analysis of DNA derived from affected tissue (skin, brain, or eye) is required for molecular confirmation; and blood, saliva, and buccal swabs will be negative. In addition, DNA sequencing must be sensitive enough to detect low-level mosaicism of a pathogenic variant (down to a variant allele frequency of 1%-2%.) In part due to the challenge of rendering a diagnosis, the prevalence of ECCL is unknown and has only been reported in approximately 85 individuals.[12] Skin manifestations include nevus psiloliparus, nodular skin tags, and alopecia.[12] Choristomas are seen in approximately 80% to 85% of people with ECCL, and intracranial lipomas in approximately 65%.[12] It is suspected that vascular anomalies, such as leptomeningeal angiomatosis, also may be common.12 People

with ECCL have a higher risk of developing brain tumors—especially low-grade gliomas—and fatty lipomas of the spinal cord compared to the general population.[12]

The particular pathogenic variants in the *FGFR1* gene that have been identified to cause ECCL are c.1638C>A (p.Asn546Lys) and c.1966A>G (p.Lys656Glu).[12,13] These activating mutations within the tyrosine kinase domain of *FGFR1* are also associated with human malignancy, including CNS tumors.[13]

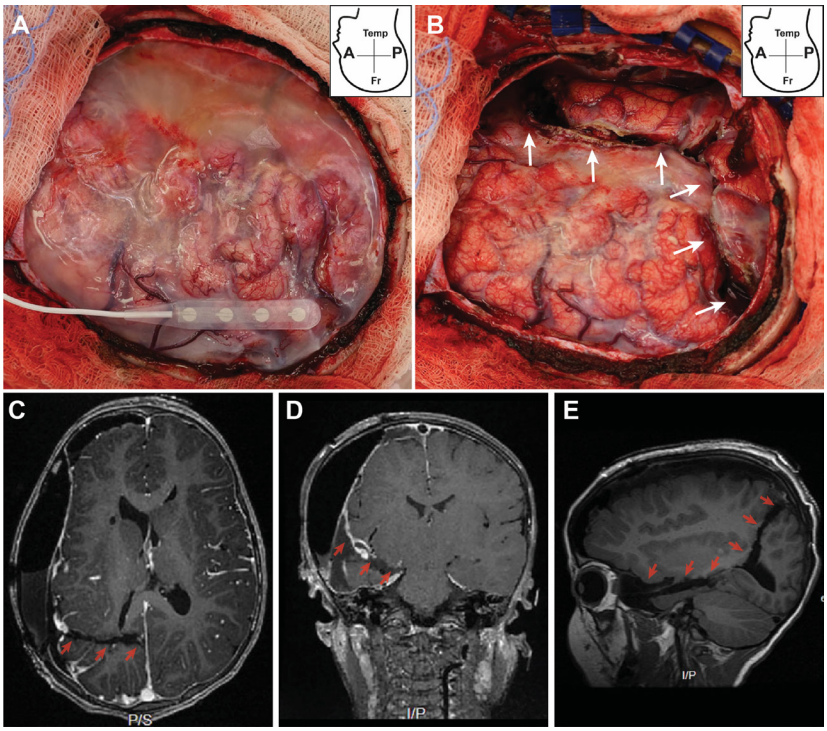
The patient in our case was found to have the pathogenic mutation c.1638C>A (p.Asn546Lys) in the *FGFR1* gene. This mutation has been documented in other pediatric patients who presented with variable manifestations of ECCL. A genetic sequencing study of 5 pediatric patients with ECCL found 3 to have the c.1638C>A (p.Asn546Lys) mutation in the *FGFR1* gene. Among these 3 patients, all had nevus psiloliparus, subcutaneous lipoma, skin tags, alopecia, and choristoma; 2 had intracranial lipomas; and 1 had both seizures and delayed neurocognitive development.[13]

Another case report described a pediatric patient with the c.1638C>A (p.Asn546Lys) *FGFR1* mutation who presented with ophthalmologic (dermolipoma, hypertelorisms), cutaneous (skin tags, potential nevus psiloliparus that was not confirmed by biopsy), and CNS (seizures, arachnoid cysts, intracranial lipomas) manifestations.[14] The variable presentations among these patients—all with ECCL and the same pathogenic mutation—demonstrate the degree to which the mosaicism of this somatic mutation contributes to the phenotype and severity of the disease and suggests that the presentation of ECCL is likely broader than initially thought. The activating *FGFR1* gene mutations likely have a role in tumorigenesis, and determination of the underlying genetic mutation in these patients may aid in selecting targeted clinical management, should the patient develop a tumor.[13]

The differential diagnosis for medically refractory epilepsy in children is broad and may include structural, genetic, or metabolic etiologies, as well as potential epilepsy syndromes.[2] Imaging is an essential component in the workup of these cases. In our case, prior to surgery, it was suspected that the patient had SWS without cutaneous manifestations. Two pediatric epilepsy centers concurred with this diagnosis. As discussed, this patient was confirmed to have ECCL rather than SWS without cutaneous manifestations. It has been hypothesized that vascular abnormalities in the CNS may be common in patients with ECCL.[12]

While a diagnosis of SWS without cutaneous manifestations or ECCL prior to surgery would have led to the same recommendation for surgical intervention for this patient, differentiating these 2 conditions is important for long-term health surveillance. Because ECCL is associated with an increased risk of developing low-grade gliomas and fatty lipomas of the spinal cord, serial neuroimaging of the brain and spinal cord for these findings is recommended. SWS is not associated with an increased risk of developing low-grade gliomas and fatty lipomas of the spinal cord. Therefore, we recommend that clinicians consider both ECCL and SWS without cutaneous manifestations in the setting of progressive, refractory, focal epilepsy, and vascular abnormalities in the CNS on imaging, and we suggest genetic testing of biopsied tissue to confirm the diagnosis.

Figure 3. Operative and Magnetic Resonance Imaging of Surgical Resection



A. Surgical exposure for the posterior hemispheric disconnection. Abnormal leptomenigeal surface evident on gross examination. A 1 x 4 lead is placed across the motor strip for neurophysiological monitoring of motor function.

B. Surgical disconnection of the posterior quadrant involves disconnection across the temporal, parietal and occipital lobes (white arrows).

C and D. Axial and coronal postoperative MRI indicates the parietal-occipital and temporal disconnections (red arrows), respectively.

E. Complete temporal-parietal-occipital disconnection (red arrows) demonstrable on postoperative sagittal magnetic resonance imaging.

CONCLUSIONS

Congenital leptomeningeal enhancement is commonly found in Sturge-Weber syndrome but may be seen in other neurocutaneous syndromes, such as ECCL. Hemispheric dysplasia should raise suspicion for a neurocutaneous syndrome, even without oculocutaneous stigmata. We recommend considering next generation sequencing for patients with a suspected neurocutaneous syndrome with atypical findings. A genetic diagnosis can be important for targeted surveillance in these patients.

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